A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP13708.

Comment on "A Nested Case–Control Study of Serum Per- and Polyfluoroalkyl Substances and Testicular Germ Cell Tumors among U.S. Air Force Servicemen"

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https://doi.org/10.1289/EHP13708

Refers to https://doi.org/10.1289/EHP12603 and https://doi.org/10.1289/EHP13212

We read with interest the recently published paper by Purdue et al.[1] and its accompanying Invited Perspective by Steenland.[2] Purdue et al. conducted a nested case–control study of 530 active-duty U.S. Air Force servicemen, their serum concentrations of nine per- and polyfluoroalkyl substances (PFAS), and their diagnoses of testicular germ cell tumors (TGCT) between 1990 and 2018. Using conditional logistic regression on a second prediagnostic sample of 187 case–control matched pairs, they reported a positive association with serum perfluorooctanesulfonate (PFOS) concentration and TGCT. The odds ratio, comparing the fourth to the first quartile, was 2.6 (95% confidence interval: 1.1, 6.4) when adjusted for military ranking and number of deployments. The overall trend across these quartiles was $p_{trend} = 0.02$. There was no association between perfluorooctanoate (PFOA) and TGCT in this study.

Both Purdue et al.[1] and Steenland[2] cited limited toxicological data related to PFOS and testicular tumors. Neither of these authors considered the study results by Thomford,[3] later summarized by Butenhoff et al.[4] from a 2-year Good Laboratory Practice oral bioassay in Sprague-Dawley rats with PFOS. Because of the null findings on the testes, Thomford's testicular tumor incidence data were not presented or discussed in detail by Butenhoff et al.[4]

As two of the co-authors (S.C. and G.W.O.) of Butenhoff et al.,[4] we take this opportunity to share the testicular tumor incidence data from the original study report.[3] Table 1 presents the neoplastic tumor data for male rat testes excerpted from this 2-year bioassay.

In Table 1, groups 1–5 corresponded to dietary potassium PFOS doses at 0, 0.5, 2, 5, and 20 ppm, respectively. Group 6 received 20 ppm for 1 year followed by control diet for another year. At terminal sacrifice, Thomford[3] reported mean serum PFOS concentrations (ng/mL) for groups 1–5, respectively, of 12, 1,310, 7,600, 22,500, and 69,300. There was no effect on testicular tumors by PFOS treatment, and the overall trend was not statistically significant ($p_{trend} = 0.4583$).

Although both Purdue et al.[1] and Steenland[2] suggested additional epidemiological research is needed, the data from this 2-year bioassay, in which the serum PFOS concentrations were much higher in magnitude than the levels reported by Purdue et al.,[1] did not support a PFOS-related effect on testicular tumors in rats.

Editor's Note: In accordance with journal policy, Purdue et al. and Steenland were invited to respond to this letter. They chose not to do so.

Table 1. Results of statistical analyses of neoplastic lesions in male rats (transcribed from text Table 5 on page 79 of Thomford[3]).

		Group					
	Incidence	1 (Control)	2 (Low)	3 (Mid)	4 (Mid-high)	5 (High)	6 (High recovery)
Testis (interstitial cell tumor, benign)[a]	Fatal incidence (*n*)	0	0	0	0	0	0
	Incidental incidence (*n*)	1	1	2	2	1	1
	Total incidence	1/60	1/50	2/50	2/50	1/60	1/39
Testis (interstitial cell tumor, malignant)[a]	Fatal incidence (*n*)	0	0	0	0	0	0
	Incidental incidence (*n*)	0	0	0	1	0	0
	Total incidence	0/60	0/50	0/50	1/50	0/60	0/39
Testis (interstitial cell tumor, benign/malignant)	Fatal incidence (*n*)	0	0	0	0	0	0
	Incidental incidence (*n*)	1	1	2	3	1	1
	Total incidence	1/60	1/50	2/50	3/50	1/60	1/39
One-sided *p*-value		0.4583+	NA	NA	0.3760+	NA	NA

Note: NA, not analyzed (for the comparison of that group vs. control).
[a]Incidences across groups do not meet selection criterion.

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The authors are employees of 3M Company, a former manufacturer of PFOA- and PFOS-related materials, which supported the work reported in the article.

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